UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,220	01/21/2000	John F. Reidhaar-Olson	16528A-038900US	5568

7590 07/17/2002

VICKI G. NORTON, ESQ.
BROBECK, PHLEGER AND HARRISON LLP
12390 EL COMINO REAL
SAN DIEGO, CA 92130

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	18

DATE MAILED: 07/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/489,220	Reidhaar-Olson, J.
Examiner	**Group Art Unit**
Lu, Frank	1634

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 4-29-02.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-19 and 28-30 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-19 and 28-30 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☒ Other Detailed Action

Office Action Summary

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on April 29, 2002 has been entered as Paper No:17. The claims pending in this application are claims 1-30 with claims 20-27 withdrawn from consideration as the result of the restriction requirement. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

Drawings

2. Although applicant's request that " applicant will provide formal drawings upon notification of allowable subject matter" was granted by the examiner in previous office, the office policy now (see attachment) required applicant to submit a proposed drawing correction as stated on FORM PTO-948 (Rev. 8-98) in Paper No. 7 in reply to this Office action. Note that failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

Election/Restriction

3. This application contains claims 20-27 drawn to an invention nonelected with traverse in Paper No. 4. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-19 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the expression level of determining gene expression of certain combination of two or more nucleic acids listed in claims 1 and 28, does not reasonably provide enablement for determining gene expression of the combination of any two or more nucleic acids listed in claims 1 and 28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance to show that a test cell contains all nucleic acids listed in claims 1 and 28. While the relative skill in the art is very high (the Ph.D. degree

with laboratory experience), there is no predictability whether the combination of any two or more nucleic acids listed in claims 1 and 28 can be used in the methods recited in claims 1 and 28.

The invention relates to a method for detecting a toxic response and a method identifying potential toxicants. The specification provides a general guidance to determining gene expression in response to a toxic response (see whole specification). However, the specification does not provide a guidance to determining gene expression of the combination of any two or more nucleic acids listed in claims 1 and 28 in response to a toxic response. A prior art search did not find a cell that contained all nucleic acids listed in claims 1 and 28. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. These undue experimentation at least included to find a cell that contained all nucleic acids listed in claims 1 and 28.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 2-19 are dependent on claim 1.

8. The term "Glutathione-S-transferase-like" in claims 1 and 9 is a relative term which renders the claim indefinite. The term "Glutathione-S-transferase-like" is not defined by the

claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

9. Claim 16 is rejected as vague and indefinite because it is unclear how a probe assay in claim 16 corresponds to step (b) of claim 1. For example, what is the composition of the probe assay? Does this probe assay comprise two or more genes in claim 1 or does this probe assay comprise one or more hybridization probes of two or more genes in claim 1? Please clarify.

Claim Rejections - 35 U.S.C. § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 9, 11, 14, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Nemoto *et al.,* (Eur. J. Biochem. 233, 1-8, 1995).

Nemoto *et al.,* teach to make Glutathione-S-transferase (GST) and GST-HSP 90α (GST-heat shock protein 90) fusion protein. GST and GST-HSP 90α were in lanes 1 and 7 of Figure 1 (page 2). This has been well known that GST and GST-fusion protein were made by IPTG induction (see Nemoto *et al.,* J. Steroid Biochem. Molec. Biol. 50, 225-233, 1994, especially see page 226, right column, fourth paragraph). Note that: (1) Glutathione-S-transferase (GST) can be considered as Glutathione-S-transferase-like protein; and (2) although Nemoto *et al.,* did not show that the expressions of GST and GST-HSP 90α in control sample as described claim 1, in

the absence of convincing evidence to the contrary the claimed invention, these limitations was considered as inherent to the reference taught by Nemoto *et al.,* since no GST protein was expressed in the absence of IPTG. IPTG could be considered as a toxic material and the expression levels of nucleic acids could be considered either at the transcriptional or the translational level.

Therefore, Nemoto *et al.,* teach all limitations recited by claims 1, 9, 11, 14, 18, and 19.

Claim Rejections - 35 U.S.C. § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-11, 14, 15, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diel *et al.,* (J. Steroid Biochem. Molec. Biol. 55, 363-373, 1995) in view of and Fagan *et al.,* (J. Biol. Chem. 264, 20513-20517, 1989).

Diel *et al.,* teach identification of estrogen regulated genes in Fe33 rat hepatoma cells by differential display polymerase chain reaction. Three genes of known sequences including insulin-like growth factor binding protein-1 (IGFBP-1) were detected by the ddRT-PCR approach. Effects of ethinyl estradiol on the mRNA levels of these genes were confirmed by "Northern-blot" analysis. If given in combination with dexamethasone and glucagon, ethinyl estradiol caused 40-fold increases in the mRNA steady state level of IGFBP-1 in Fe33 cells 24 h

after addition of hormone (see abstract in page 363 and Figures 1, 3, and 4 in pages 365, 367, and 368).

Fagan *et al.,* teach regulation of ornithine aminotransferase (OAT) in retinoblastomas. They found that two retinoblastoma strains, Y79 and RB355, had approximately 5-fold increases in OAT protein and mRNA levels. Note that OAT is expressed in most tissues of the rat, liver, kidney, and retina had the highest levels of OAT activity (see abstract in page 20513, Figures 1 and 2 in pages 20514 and 20515).

Diel *et al.,* and Fagan *et al.,* do not disclose analyzing two or more different genes, ie. insulin-like growth factor binding protein-1 and ornithine aminotransferase in a single assay.

However, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have examined estrogen effects in the regulation of expression of two or more known genes in a liver originated cell in view of the references of Diel *et al.,* and Fagan *et al.*. One having ordinary skill in the art would have motivated to modify the methods of Diel *et al.,* and Fagan *et al.*. and combine above methods together in order to investigate the estrogen effects on two or more known genes from a liver originated cell since two or more genes in claims 1 and 5-10 could be found in liver and was known in the art at the time the invention was made. For example, enzymes for glucose and lipid metabolism (ie. pyruvate dehydrogenase and lactate dehydrogenase), proteins for oxidation phosphorylation (ie.cytochrome c1) (see any Biochemistry textbook), IGFBP-1, OAT, and defender against cell defender against cell death 1 (see Hong et al., Mol. Cell. Biol. 17, 2151-2157, 1997, especially Figure 5) existed in liver. One having ordinary skill in the art at the time

the invention was made would have been a reasonable expectation of success to investigate the estrogen effects on two or more known genes from a liver originated cell.

Response to Arguments

In page 8, last paragraph bridging to page 11, first paragraph of applicant's remarks, applicant argued that: (1) " [S]ince one skilled in the art interested in measuring the response of mRNA levels to a toxicant would likely be particularly interested in such a response in the liver, such information would be seen as teaching away from selecting the OAT to measure toxic response."; and (2) " the Examiner has failed to provide any motivation for one skilled in the art to combine the two references and simultaneously measure the response of IGFBP-1 and OAT in response to estrogen, or in response to any other chemical stimulus." and "does not explain why these particular two genes in liver cells might be selected.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the examiner agreed with applicant "one skilled in the art interested in measuring the response of mRNA levels to a toxicant would likely be particularly interested in such a response in the liver" . Second, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since a lot of genes in liver including enzymes

for glucose and lipid metabolism and proteins for oxidation phosphorylation were cloned and these known genes were generally available to one of ordinary skill in the art at the time the invention was made, it would have been *prima facie* obvious to one having ordinary skill in the art to have examined estrogen effects in the regulation of expression of two or more known genes in a liver originated cell in view of the references of Diel *et al.,* and Fagan *et al.,* in order to investigate the estrogen effects on two or more known genes from a liver originated cell. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to investigate the estrogen effects on two or more known genes from a liver originated cell. Third, the examiner did not need "explain why these particular two genes in liver cells might be selected." since, in the examiner's opinion, one having ordinary skill in the art could select any two genes including genes recited in claim 1 to investigate the estrogen effects.

14. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diel *et al.,* (1995) and Fagan *et al.,* (1989) as applied to claims 1-11, 14, 15, 18, and 19 above, and further in view of Desjardins *et al.,* (Cancer Lett., 131, 201-207, 1998).

The teachings of Diel *et al.,* and Fagan *et al.,* have been summarized previously, *supra.*

Diel *et al.,* and Fagan *et al.,* do not disclose to use HepG2 cells.

Desjardins *et al,* do teach to study the expression of different genes in the presence of a toxic material using HepG2 cells (see page 201, abstract). Note that HepG2 cells are human hepatoma cells (see page 201, left column).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have examined estrogen effects in the regulation of expression of two or more known genes in HepG2 cells in view of the reference of Desjardins *et al.*. One having ordinary skill in the art would have motivated to modify the methods of Diel *et al.*, and Fagan *et al.*, and combine above methods together because the simple replacement of one kind of liver cell from another kind of liver cell (i.e. HepG2 cell) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. Furthermore, the motivation to make the substitution cited above, arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 11, last paragraph bridging to page 12, first paragraph of applicant's remarks, applicant argued that applicant was not clear of the relevance of reference of Desjardins *et al.*, to claims 12 and 13.

This arguments has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, reference of Desjardins *et al.*, was related to the effect of a toxic

compound on the expression of different liver genes and was considered as an analogous art of the references of Diel *et al.,* and Fagan *et al.*. Second, since HepG2 cell was a liver originated cell, the simple replacement of liver cell used in f the references of Diel *et al.,* and Fagan *et al.*. from HepG2 cell (another kind of liver cell) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

15. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Diel *et al.,* (1995) and Fagan *et al.,* (1989) as applied to claims 1-11, 14, 15, 18, and 19 above, and further in view of Schena *et al.*, (Proc. Natl. Acad. Sci. USA, 93, 10614-10619, 1996).

Note that this rejection was made in view of the ambiguity of claim 16.

The teachings of Diel *et al.,* and Fagan *et al.,* have been summarized previously, *supra.*

Diel *et al.,* and Fagan *et al.,* do not disclose to use a cDNA array.

Schena *et al.*, teach parallel human genome analysis using microarray-based expression. In this study, a total of 1056 cDNA, representing 1046 human clones and 10 *arabidopsis* control, were arrayed in 1.0-cm^2 areas (page 10614, right column, second paragraph). Microassays were used to examine the cellular effects of phenol ester treatment in cultured human T (Jurkat) cells. Untreated and phenol ester-treated cells were harvested and lysed, and total mRNA from the two cell samples was labeled by reverse transcriptase incorporation of fluorescein- and cy5-dCTP, respectively. In a second set of labeling reactions, the fluorescent groups were "swapped" such that sample from control and phenol ester-treated samples were labeled with cy5- and

fluorescein-dCTP, respectively (page 10616, Figure 2B). Each pair of fluorescent probes was hybridized to a 1056-element microarray. A total of six array elements displayed ≥2.0 fold elevated signals with probes from phorbol ester-treated cells relative to control samples (page 10617, left column, second paragraph and Figure 2B in page 10616). The identity of the phenol ester-induced genes were confirmed by DNA sequencing (page 10617, left column, third paragraph).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have examined estrogen effects in the regulation of expression of two or more known genes in a cDNA array comprising two or more known cDNA clones in view of the reference of Schena *et al.*. One having ordinary skill in the art would have motivated to modify the methods of Diel *et al.,* and Fagan *et al.,* and combine above methods together because the method to make a cDNA array and genes listing in claim 1 were in the art at the time the invention was made and the simple replacement of one well known detection method from another well known detection method (i.e. cDNA array) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. Furthermore, the motivation to make the substitution cited above, arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 12, third paragraph of applicant's remarks, applicant argued that the reference of Schena *et al.*, " is distinguishable from the instant invention as the sequence present on the microarray of Schena *et al.*, were selected randomly. The DNA sequence used in the instant invention are specifically set forth in claim 1." .

This arguments has been fully considered but it is not persuasive toward the withdrawal of the rejection because claim 16 does not limit that the DNA sequence on a probe array are specifically set forth in claim 1. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

16. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Diel *et al.*, (1995) and Fagan *et al.*, (1989) as applied to claims 1-11, 14, 15, 18, and 19 above, and further in view of Zamorano *et al.*, (Neuroendocrinology 63, 397-407, May 1996).

The teachings of Diel *et al.*, and Fagan *et al.*, have been summarized previously, *supra.*

Diel *et al.*, and Fagan *et al.*, do not disclose to quantitative RT-PCR.

Zamorano *et al.,* reviewed quantitative RT-PCR. One of advantage of this technique is to measure mRNA levels in small amounts of tissue or even in single cells (page 406, left column, second paragraph).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have examined estrogen effects in the regulation of gene expression of two or more known genes using quantitative RT-PCR in view of the reference of Zamorano *et al.*. One having ordinary skill in the art would have motivated to modify the methods of Diel *et al.,* and Fagan *et al.,* and combine above methods together because the simple replacement of one well known detection method from another well known detection method (i.e. quantitative RT-PCR, see Zamorano *et al.,* for the cited references) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. Furthermore, the motivation to make the substitution cited above, arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 12, last paragraph bridging to page 13, first paragraph of applicant's remarks, applicant argued that "[T]he examiner has failed to provide a motivation to combine the particular genes set forth in claim 1 when measuring a toxic response by means of RT-PCR." since "[Z]amorano *et al.,* are silent as how to select the set of genes to be used for an array." .

This arguments has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, the examiner had provided a motivation to combine the particular genes set forth in claim 1 (see above). Second, although "[Z]amorano *et al.,* are silent as how to select the set of genes to be used for an array." , the motivation was from the simple replacement of one well known detection method from another well known detection method (i.e. quantitative RT-PCR.

17. Claim 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Diel *et al.,* (1995), Fagan *et al.,* (1989) as applied to claims 1-11, 14, 15, 18, and 19 above, and further in view of Li *et al.,* (Cell Biol. Int. Rep. 13, 619-624, 1989) and Martin *et al.,* (BioTechnique 21, 520-524, September 1996).

The teachings of Diel *et al.*, and Fagan *et al.,* have been summarized previously, *supra.*

Li *et al.,* teach to examine estrogen-induced expression of mouse lactate dehydrogenase A gene using mouse lactate dehydrogenase A promoter and cat fusion gene (see forth paragraph of page 620 and first paragraph in page 621).

Diel *et al.*, Fagan *et al.*, and Li *et al.*, do not disclose the determination of gene expression using different reporter systems.

Martin *et al.*, do teach the determination of gene expression using different reporter systems (ie. luciferase and beta-galactosidase). Note that both independent and combined (Dual-Light) detection methods for cells cotransfected with luciferase and beta-gal reporter genes are sensitive enough to determine gene expression (see abstract in page 520 and Table 1 in page 522).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have examined estrogen effects in the regulation of gene expression of three or more different genes such as IGFBP-1, OAT, lactate dehydrogenase A using promoters from different genes using different reporter systems in view of the references of Li *et al.*, and Martin *et al.*. One having ordinary skill in the art would have motivated to modify and combine above methods together because: (1) promoters of at least three of genes listed in claims 28-30 were known in the art at the time the invention was made (i.e. OAT and IGFBP-1, see Biochim. Biophys. Acta, 1132, 214-218, 1992 and Endocrinology 134, 736-743, 1994); and (2) the simple replacement of one well known detection method from another well known detection method (i.e. using reporter gene) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. Furthermore, the motivation to make the substitution cited above, arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common

known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 13, fourth paragraph bridging to page 14, first paragraph of applicant's remarks, applicant argued that "the examiner has filed to provide a motivation to combine the particular gene listed supra or listed in claim 1 out of the hundreds or thousands of available genes, nor do the above references suggest using such a means to measure gene expression for use in screening for possible toxicants.".

This arguments has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, the examiner had provided a motivation to combine the particular gene listed (see above). Second, in the examiner's opinion, one having ordinary skill in the art could select any three genes including genes recited in claim 28 to investigate the estrogen effects.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. No claim is allowed.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
July 5, 2002

ETHAN C. WHISENANT
PRIMARY EXAMINER